Complete Summary

GUIDELINE TITLE

Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.

BIBLIOGRAPHIC SOURCE(S)

Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, Hoffenberg EJ, Horvath K, Murray JA, Pivor M, Seidman EG. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2005 Jan;40(1):1-19. [206 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Celiac disease

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Risk Assessment
Treatment

CLINICAL SPECIALTY

Endocrinology
Family Practice
Gastroenterology
Medical Genetics
Nutrition
Pathology
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Dietitians
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To develop a clinical practice guideline for early diagnosis and treatment of celiac disease in children

TARGET POPULATION

Infants and children with suspected celiac disease in inpatient and outpatient settings

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

1. Medical history (gastrointestinal and non-gastrointestinal manifestations of celiac disease [CD])
2. Physical examination
3. Measurement of immunoglobulin A (IgA) antibody to human recombinant tissue transglutaminase (TTG)
4. Consultation with pediatric gastroenterologist
5. Endoscopic duodenal biopsy
6. Consideration of IgA antibody to endomysium (EMA), human leukocyte antigen (HLA) type, and a repeat biopsy if needed

Note: The use of antigliadin antibody (AGA) IgA and AGA immunoglobulin G (IgG) tests were considered but are no longer recommended.

Treatment/Monitoring

1. Gluten-free diet (GFD)
2. Nutritional education by a dietitian
3. Periodic assessment of symptoms, diet adherence, and serology
4. Evaluation for other causes of symptoms if needed

MAJOR OUTCOMES CONSIDERED

- Prevalence of celiac disease (CD) in children
- Mortality and other risks in patients with untreated CD
- Adherence to a gluten-free diet in children with CD

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

To develop evidence-based guidelines the following search strategy was used. Articles published from 1966 to February 2003 were identified using the medical subject heading (MESH) "Celiac Disease" through searches in PubMed (http://www.ncbi.nih.gov/entrez/query.fcgi), the Database of Abstracts of Reviews of Effects (DARE) (http://www.york.ac.uk/inst/crd/darehp.htm) and the Cochrane Database of Systematic Reviews (through OVID, Ovid Technologies, Inc. www.ovid.com). Letters to the editors, editorials, case reports, and nonsystematic reviews were not included.

NUMBER OF SOURCE DOCUMENTS

No articles were identified in the Cochrane database, and four were identified through the Database of Abstracts of Reviews of Effects (DARE). The first subcategory used in PubMed was diagnosis. A total of 317 articles were found, 285 in English and 167 of those limited to children. In the subcategory of prognosis, 117 articles were found, with 86 limited to English and 38 of those limited to children. In the subcategory of therapy, a total of 1503 articles were found, with 1143 in English and 486 limited to children. Thirty articles were duplicated in more than one category. A second search was performed in September 2003, and an additional 73 articles were identified.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Articles were evaluated by two committee members using written criteria developed by Sackett et al. (http://www.cebm.net/levels_of_evidence.asp; accessed on 2/3/2004). Twenty-nine randomly chosen articles were independently reviewed by two members of the committee with expertise in clinical epidemiology. Concordance using the criteria was 82%.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Nominal Group Technique)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Committee based its recommendations on integration of the literature review combined with expert opinion when evidence was insufficient. Consensus was achieved through the Nominal Group Technique, a structured, quantitative method.

Using the methods of the Canadian Preventive Services Task Force, the quality of evidence of each of the recommendations made by the Celiac Disease Guideline Committee was determined and is summarized.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The guideline developers reviewed published cost analyses.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Who to Test?

Celiac disease (CD) is an immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals. It occurs in symptomatic children and adolescents with gastrointestinal and nongastrointestinal symptoms. It also occurs in some asymptomatic individuals who have conditions that are associated with CD. Based on a number of studies in Europe and the United States, the prevalence of CD in children between 2.5 and 15 years of age in the

general population is 3 to 13 per 1,000 children, or approximately 1:300 to 1:80 children.

Numerous studies demonstrate that children with CD frequently have gastrointestinal (GI) symptoms such as diarrhea with failure to thrive (FTT), abdominal pain, vomiting, constipation, and abdominal distension. However, there is little information currently available about the precise prevalence of CD in children with these specific types of GI symptoms. There is strong evidence for an increased occurrence of CD in children with dermatitis herpetiformis, dental enamel defects, type 1 diabetes, immunoglobulin A (IgA) deficiency, Down syndrome, Turner syndrome, Williams syndrome, and first-degree relatives of patients with CD. There is moderate evidence for an increased prevalence of CD in children with short stature and some evidence for an increased prevalence of CD in children with autoimmune thyroiditis. There is evidence that anemia is common in children with CD, and an increased prevalence of unexplained anemia as a presenting feature is well described in adults with CD. Other conditions that have been described in association with CD include a variety of neurologic disorders; however, the evidence for these associations in children is poor.

It is recommended that CD be an early consideration in the differential diagnosis of children with FTT and persistent diarrhea. In addition, it is recommended that CD be considered in the differential diagnosis of children with other persisting GI symptoms, including recurrent abdominal pain, constipation and vomiting. Testing is recommended for children with nongastrointestinal symptoms of CD (dermatitis herpetiformis, dental enamel hypoplasia of permanent teeth, osteoporosis, short stature, delayed puberty and iron-deficient anemia resistant to oral iron). Testing is also recommended for asymptomatic children who have conditions associated with CD (type 1 diabetes mellitus, autoimmune thyroiditis, Down syndrome, Turner syndrome, Williams syndrome, selective IgA deficiency, and first-degree relatives of celiac patients). It is recommended that testing of asymptomatic children who belong to groups at risk begin around 3 years of age provided they have had an adequate gluten-containing diet for at least 1 year before testing.

There is good evidence that in certain groups (type 1 diabetes, first-degree relatives of affected individuals, and Down syndrome) some individuals who initially have a negative serological test may subsequently develop a positive test on repeat testing over a period of years and have biopsies compatible with CD. Therefore, it is recommended that asymptomatic individuals with negative serological tests who belong to groups at risk be considered for repeat testing at intervals. As there is no good evidence that CD is more common in children with autism, there is no indication to routinely test patients with autism for CD.

How to Test?

Based on the current evidence and practical considerations, including accuracy, reliability, and cost, measurement of IgA antibody to human recombinant tissue transglutaminase (TTG) is recommended for initial testing for CD. Although as accurate as TTG, measurement of IgA antibody to endomysium (EMA) is observer dependent and therefore more subject to interpretation error and added cost. Because of the inferior accuracy of the antigliadin antibody tests (AGA), the use of AGA IgA and AGA IgG tests is no longer recommended for detecting CD.

Individuals with CD who are also IgA deficient will not have abnormally elevated levels of TTG IgA or EMA IgA. The occurrence of both CD and IgA deficiency in the same individual appears to be rare in asymptomatic individuals (approximately 1:8,500 of the general population) but is more likely in symptomatic children with CD (approximately 2%). Therefore, when testing for CD in children with symptoms suspicious for CD, measurement of quantitative serum IgA can facilitate interpretation when the TTG IgA is low. In individuals with known selective IgA deficiency and symptoms suggestive of CD, testing with TTG IgG is recommended. Even when serological tests for CD are negative, in children with chronic diarrhea or FTT and in those belonging to a group at risk (e.g., selective IgA deficiency or a positive family history of CD) who have symptoms compatible with CD, an intestinal biopsy can be helpful to identify the unusual case of seronegative CD or to detect other mucosal disorders accounting for the symptoms.

It is recommended that confirmation of the diagnosis of CD require an intestinal biopsy in all cases. Because the histologic changes in CD may be patchy, it is recommended that multiple biopsy specimens be obtained from the second or more distal part of the duodenum. There is good evidence that villous atrophy (Marsh type 3) is a characteristic histopathologic feature of CD. The presence of infiltrative changes with crypt hyperplasia (Marsh type 2) on intestinal biopsy is compatible with CD but with less clear evidence. Diagnosis in these cases is strengthened by the presence of positive serological tests (TTG or EMA) for CD. In the event the serological tests are negative, other conditions for the intestinal changes are to be considered and, if excluded, the diagnosis of CD is reconsidered. The presence of infiltrative changes alone (Marsh type 1) on intestinal biopsy is not specific for CD in children. Concomitant positive serological tests for CD (TTG or EMA) increases the likelihood such an individual has CD. In circumstances where the diagnosis is uncertain, additional strategies can be considered, including determination of the human leukocyte antigen (HLA) type, repeat biopsy, or a trial of treatment with a gluten-free diet (GFD) and repeat serology and biopsy.

The diagnosis of CD is considered definitive when there is complete symptom resolution after treatment with a strict GFD in a previously symptomatic individual with characteristic histologic changes on small intestinal biopsy. A positive serological test that reverts to negative after treatment with a strict GFD in such cases is further supportive evidence for the diagnosis of CD.

Who to Treat?

Treatment with a GFD is recommended for all symptomatic children with intestinal histopathologic abnormalities that are characteristic of CD. Clinical experience has demonstrated that children with persistent diarrhea and poor weight gain resulting from CD have complete resolution of symptoms on treatment with a GFD. There is good evidence that treatment with a GFD reverses the reduced bone mineralization in children with CD and decreases the rate of spontaneous abortions and frequency of low birth weight infants in adult women with CD. Epidemiological evidence suggests treatment of CD can decrease the risk for some intestinal cancers and lower mortality rates to that of the general population. The evidence that early treatment of CD prevents the onset of other autoimmune diseases is weak.

Treatment with a GFD is also recommended for asymptomatic children who have a condition associated with CD and characteristic histologic findings on small intestinal biopsy. In patients with type 1 diabetes who otherwise have no symptoms associated with CD, there is little evidence to demonstrate that a GFD improves their diabetes in the short term. The intermediate and long-term benefits to diabetes care of treating such patients with a GFD are not known. There are no studies on the benefits of treating asymptomatic CD in individuals with other associated conditions.

How to Treat?

A GFD for life remains the only scientifically proven treatment available for symptomatic individuals with CD. It is recommended that treatment be started only after the diagnosis has been confirmed by intestinal biopsy according to the diagnostic algorithms presented in this guideline.

The Celiac Disease Guideline Committee endorses the recently published American Dietetic Association guidelines (a document produced by members of the Canadian and United States dietetic societies) for the treatment of CD. However, given the dynamics of this field, these recommendations require periodic review and modification in light of new scientific evidence.

There is evidence to demonstrate that even small amounts of gluten ingested on a regular basis by individuals with CD can lead to mucosal changes on intestinal biopsy. Previously, products containing less than 200 ppm were regarded as gluten free. Currently, a limit of 20 ppm is being considered in the proposed Codex Alimentarius as defining gluten free. Controversy surrounding what constitutes a GFD is the result of inaccurate techniques for detecting gluten and the lack of solid scientific evidence for a threshold of gluten consumption below which no harm occurs. Management of a GFD is facilitated by ongoing collaboration between patients, health care professionals, and dieticians.

Most newly diagnosed children will tolerate ingestion of lactose, particularly in moderate amounts; therefore dietary lactose restriction is not usually necessary. Young children with more severe disease may benefit from a lactose-free diet initially.

How to Monitor?

It is recommended that children with CD be monitored with periodic visits for assessment of symptoms, growth, physical examination, and adherence to a GFD. There is little evidence on the most effective means of monitoring patients with CD. The Celiac Disease Guideline Committee recommends measurement of TTG after 6 months of treatment with a GFD to demonstrate a decrease in antibody titer as an indirect indicator of dietary adherence and recovery. Measurement of TTG is also recommended in individuals with persistent or recurrent symptoms at any time after starting a GFD, as a rise in antibody levels suggests dietary non-adherence. In the asymptomatic patient measurement of TTG at intervals of 1 year or longer may serve as a monitor of adherence to the GFD.

Studies in children have shown that adherence to a GFD is reported by 45 to 81% of patients. These may be overestimates, as some patients reporting strict

adherence have abnormal small intestinal histology. A complete lack of adherence is reported by 6 to 37% of patients. These may be underestimates, as patients are reluctant to admit that they are not following medical advice. Based on limited data, the rate of adherence in asymptomatic patients who were detected as part of a population screening is similar to the rate of adherence in patients who had symptoms that led to the detection of CD.

Evidence demonstrates that about 95% of children with symptoms of CD, a biopsy characteristic (Marsh type 3) of CD, and resolution of symptoms on a GFD do in fact have CD. Therefore, additional biopsies for confirmation of the diagnosis are not recommended in such cases.

Algorithms for the Evaluation and Management of Infants and Children with Suspected Celiac Disease

(In the following text, references to figures and boxes refer to the algorithms presented in the original guideline document.)

Evaluation of the Symptomatic Child

Identification of children with symptoms who need an intestinal biopsy to diagnose CD requires that health care professionals appreciate the variable clinical manifestations of the disorder. This includes recognition of both gastrointestinal and non-gastrointestinal manifestations (Figure 1, Box 1; see also Table 1 in the original guideline document). After a detailed history and physical examination (Figure 1, Box 2), if CD is a consideration in the differential diagnosis, serological testing with TTG is recommended (Figure 1, Box 3). If TTG is normal, it is unlikely the child has CD, and other conditions are considered (Figure 1, Boxes 4 and 5). Symptomatic children with a positive TTG are referred to a pediatric gastroenterologist for small intestinal biopsy (Figure 1, Boxes 5 and 6). Those with histologic features of CD on biopsy are treated with a strict GFD (Figure 1, Boxes 8 and 9). If there is complete symptom resolution on a GFD, the diagnosis of CD can be considered definitive for life.

Children with symptoms who are TTG-positive but without characteristic changes of CD on small intestinal histology present a diagnostic challenge (Figure 1, Boxes 7 and 8). Possibilities in these cases include the following: the child does not have CD and the TTG was a false positive, the child has CD but the histologic changes were either not detected by the pathologist or were missed on biopsy because of the patchy nature of the disease, or a positive TTG with a truly normal biopsy represents an early stage of the disease that is manifest by seropositivity only. Under such circumstances, several strategies are available that may help establish a diagnosis (Figure 1, Box 7). These include a careful review of the original biopsy specimens by an experienced pathologist, measurement of EMA, repeating an endoscopy to obtain multiple small intestinal biopsy samples and determination of the HLA DQ2 and DQ8 genotypes. In the event the child is negative for both HLA DQ2 and DQ8, it is highly unlikely that CD is the cause of the symptoms and other conditions would be considered.

Evaluation of the Asymptomatic Child in an At-Risk Group

It is recommended that asymptomatic children who are first-degree relatives of an individual with confirmed CD and those with autoimmune and nonautoimmune conditions known to be associated with CD undergo testing for CD beginning in childhood (Figure 2, Box 1). It is recommended that testing occur after 3 years of age after the child has been on an adequate gluten containing diet for at least 1 year before testing. The initial test of choice for this purpose is the TTG (Figure 2, Box 2). For those individuals who are selective IgA deficient, measurement of TTG IgG is recommended. If the TTG is negative, it is unlikely the child has CD at that time. However, as demonstrated on interval testing in some patients with type 1 diabetes and Down syndrome, an initial negative serological test for CD does not entirely exclude the possibility the individual will develop CD later in life. Strategies for addressing this possibility include repeat TTG testing at intervals over a period of some years and at any time that the child develops symptoms compatible with CD or determining whether the child has the HLA DQ2 or DQ8 genotype (Figure 2, Boxes 3 and 4). Those who have neither of these genotypes may be reassured they are at minimal risk for CD and need no further testing. Conversely, those who are either HLA DQ2 or DQ8 positive are considered potentially at risk and may warrant later testing.

In the event the initial TTG is positive, the child is referred to a pediatric gastroenterologist for an intestinal biopsy (Figure 2, Boxes 4 and 5). If the histology is compatible with CD, the child is treated with a GFD for life (Figure 2, Boxes 7 and 8). Those with a positive TTG but without characteristic changes of CD on histology require additional strategies to clarify the situation (Figure 2, Boxes 6 and 7). These include reviewing the pathology with an experienced pathologist, repeating the endoscopy and obtaining multiple biopsies to exclude a patchy lesion, testing for EMA, and determining whether the individual has either the HLA DQ2 or DQ8 genotype (Figure 2, Box 6). In the event the child is neither HLA DQ2 nor DQ8 positive, the likelihood of having CD is extremely small and no further testing is warranted. (For patients with type 1 diabetes, see section 3.2.2 in the original guideline document.)

Treatment and Monitoring of Patients with CD

The treatment of CD is a GFD for life. Untreated CD carries a significant increased risk for both morbidity and mortality. After histologic identification of intestinal mucosal features compatible with CD (Figure 3, Box 1), it is recommended that education be provided about CD and the potential adverse health consequences associated with continued ingestion of gluten and related products. It is recommended the patient be referred to a nutritionist for education about a GFD (Figure 3, Box 2). Referral to a CD support group is also considered beneficial by providing the opportunity for emotional and psychologic support and serving as a source of information for gluten-free products available locally.

Periodic assessment by the physician and nutritionist is recommended to monitor for symptom resolution, maintenance of continued growth and development, dietary review, and repeat serological testing (Figure 3, Box 3). During these assessments health care professionals can reinforce the benefits of compliance with a strict GFD for life. Failure of the TTG level to decline over a period of 6 months after starting the GFD suggests continued ingestion of gluten or related products. In these cases there is a need for careful dietary review, looking for sources of gluten, and reinforcement of the need to remain on a strict GFD (Figure

3, Boxes 4 and 5). Normalization of TTG on repeat testing suggests compliance with the GFD. The complete resolution of symptoms in the previously symptomatic child is further supportive evidence that the patient is adhering to treatment (Figure 3, Boxes 5 and 6). These patients then receive annual assessment, providing they remain asymptomatic (Figure 3, Boxes 3 and 6).

Children whose symptoms persist or who develop symptoms again after a period of symptom resolution may be failing to adhere to treatment or may have an additional problem not related to CD (Figure 3, Boxes 6 and 7). Repeat serological testing in these cases is recommended. A positive test suggests nonadherence and requires dietary review and reinforcement of the need for compliance. A negative test suggests the symptoms are not related to CD but does not entirely exclude the possibility of CD (Figure 3, Box 7). If, after evaluation for other conditions, no alternative cause for the symptoms is identified, it is reasonable to consider repeating the intestinal biopsy to determine whether there are still changes compatible with CD.

CLINICAL ALGORITHM(S)

Algorithms are provided in the original guideline document for:

- Evaluation of the Symptomatic Child
- Evaluation of the Asymptomatic Child in an At-Risk Group
- Treatment and Monitoring of Patients with CD

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- A complete resolution of symptoms and prevention of complications of celiac disease (CD) can be achieved through implementation of a lifelong gluten-free diet (GFD) at an early stage of the disease utilizing the most effective strategy available.
- Treatment of symptomatic individuals with CD decreases the mortality rate compared with those who remain untreated. When CD is diagnosed in childhood or adolescence there appears to be no increased cancer risk, presumably because of early initiation of a GFD.

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, Hoffenberg EJ, Horvath K, Murray JA, Pivor M, Seidman EG. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2005 Jan;40(1):1-19. [206 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005 Jan

GUIDELINE DEVELOPER(S)

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition - Professional Association

SOURCE(S) OF FUNDING

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

GUIDELINE COMMITTEE

Celiac Disease Guideline Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) Web site.

Print copies: Available from NASPGHAN, PO Box 6, Flourtown, PA 19031; Telephone (215) 233-0808; Fax (215) 233-3939; E-mail: naspghan@naspghan.org.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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